UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,811	12/02/2003	Craig Basson	955-12 DIV	3344

23869 7590 04/30/2007
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,811	BASSON, CRAIG	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-29,31,33 and 34* is/are pending in the application.

4a) Of the above claim(s) *24,27 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,26,28,29,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Election filed December 8, 2006 in response to the Office Action of September 6, 2006 is acknowledged and has been entered. Claims 23-29, 31, 33-34 are pending in the application and Claims 24, 27, 34 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 23, 25-26, 28-29, 31, 33 are currently under prosecution.

2. The response to the restriction requirement of September 6, 2006 has been received. Applicant has elected claims 23, 25-26, 28-29, 31, 33 drawn to the species of (a) the method carried out *in vivo*, (b) introducing a nucleic acid that encodes the polypeptide, (c) wild-type T box sequence of TBX5 capable of binding to both the major and minor groove of target DNA, (d) a malignant cells, for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Specification

3. Spelling error informalities have been identified in the specification. For example, DESCRIPTIION" on page 4, para 0019. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where these errors may be found. Appropriate correction is required.

4. Figures 2 and 3 and the Brief Description of the Drawings are objected to because although Figure 2 is a graph showing the effect of overexpression of wild-type and mutant TBX5 isoforms on proliferation of D17 cells, there is no legend on the drawing or definition in the Description of what the lines on the graph represent, i.e. dotted or solid, what the filled circles, boxes and triangles represent.

Further, it is not possible to determine from the information in the Brief Description of Figure 3, which of the bars represent treatment and control.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23, 25-26, 28-29, 31, 33 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to a method of inhibiting proliferation of cells/malignant cells comprising introducing into said cells a nucleic acid molecule that encodes a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA.

The specification teaches that the human TBX5 protein is SEQ ID NO:1 (para 0022). The human wild-type TBX5 protein includes a T-box sequence that begins with amino acid 56 and ends with amino acid 238 of the human protein of SEQ ID NO: 1 and teaches that a useful 5' T-box sequence capable of binding to the major groove of target DNA begins at approximately amino acid 56 of the human protein of SEQ ID NO: 1 and contains a sufficient number of residues to inhibit cellular proliferation. TBX5 also includes polypeptides from species other than human (para 0024). The specification further teaches that the present invention provides a cloned nucleic acid molecule encoding any of the TBX5 protein fragments described, including functional homologs (para 0033) (thus

indicating that the term TBX5 includes functional homologs, many of which would be expected to be "wild-type" proteins) , wherein said functional homologs include proteins that shares at least 60% identity with another protein, presumably in this case SEQ ID NO:1 (para 0027). The specification particularly teaches that "A homolog of a protein fragment is considered to be a functional homolog if the homolog maintains at least some of the activity of the protein fragment" (para 0028). The specification exemplifies *in vitro* inhibition of D17 cell line proliferation by infection of said cells with vector encoding a polypeptide consisting of SEQ ID NO:1 and a vector encoding a polypeptide consisting of SEQ ID NO:1 truncated at amino acid 198 (see Examples).

Clearly, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by

> members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the introduced nucleic acid encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell, per Lilly by structurally describing a representative number of introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell required to practice the

method in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell, nor does the specification provide any partial structure of such introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell, nor any physical or chemical characteristics of the introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell nor any functional characteristics coupled with a known or disclosed correlation between structure and function other than the nucleic acid encoding a polypeptide consisting of SEQ ID NO:1 or consisting of SEQ ID NO:1 truncated at amino acid residue 198. Although the specification discloses these two species, this does not provide a description of introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell that would satisfy the standard set out in Enzo.

The specification also fails to describe the introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell by the test set out in Lilly. The specification describes only the two examples set forth above. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the introduced nucleic acids encoding a polypeptide comprising a translated 5' T-box sequence of TBX5, as defined by the specification, wherein said polypeptide contains a sufficient number of binding residues and is capable of binding to the major groove of target DNA which will inhibit the proliferation of a cell/malignant cell that is required to practice the claimed invention. Since the specification fails to adequately describe the product critical to the method, it also fails to adequately describe the claimed method.

7. If Applicant were able to overcome the rejection set forth above, Claims 23, 25-26, 28-29, 31, 33 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting, *in vitro*, the proliferation of D17 cell line cells comprising introducing into said cells a polynucleotide encoding a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA, does not reasonably provide enablement for a method of inhibiting the proliferation of a cell, a

malignant cell, comprising introducing into said cell, *in vivo*, a nucleic acid molecule that encodes a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of inhibiting the proliferation of a cell, a malignant cell, *in vivo,* comprising introducing into said cell, a nucleic acid molecule that encodes a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA, wherein the sequence is a human sequence, wherein the malignant cell is a carcinoma, osteocarcinoma, sarcoma, osteosarcoma, glioma, melanoma, myxoma, adenoma or rhabdomyoma-derived cell, wherein the cell is a metastasized cell.

This means that the claims are drawn to a method of introducing a nucleic acid into said cancer/malignant cells, a nucleic acid encoding a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA, including all of those claimed, *in vivo,* which reads on a method of treating cancer, *in vivo*.

The specification teaches that the present invention provides a method of inhibiting the proliferation of a cell, a malignant cell wherein the cell may be part of a solid tumor or a non-solid tumor (para 0048). The invention encompasses methods of use of nucleic acid molecules of the invention in regulating malignant cell growth (para 0020) by (1) introducing a nucleic acid encoding a polypeptide comprising a translated T-box sequence of TBX5 capable of binding to the major groove of target DNA, into accessible cells, (2) by expressing in the cells said

nucleic acid molecule that encodes the polypeptide, to allow for inhibition of proliferation of malignant cell types (para 0051).

The specification exemplifies the construction of viral vectors and propagation of recombinant virus comprising the entire TBX5 coding sequence, or a truncation mutant isoform, for SEQ ID NO:1(pgs 22-23). The specification further exemplifies the *in vitro* infection of D17 canine osteosarcoma cells with said construct wherein the transgenes were transcribed (para 0121 of the published application), wherein it was found that transcription and expression of full length and truncation isoform at amino acid 198 resulted in slower proliferation of D17 cells than in D17 cells transfected with control (para 0128 of the published application).

One cannot extrapolate the teaching of the specification to the scope of the claims because the art recognizes the unpredictability, pitfalls and inherent limitations of cancer therapy discovery based on *in vitro* studies. For example, Dermer (Bio/Technology, 1994, 12:320) teaches that, *in vitro*/petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly, at the time the invention was made, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in*

vivo environment involved in host-tumor and cell-cell interactions. More recently, Zips et al (In vivo, 2005, 19:1-8) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col 2).

Further, the unpredictability of the cancer therapy arts is well known and is exemplified by Gura (Science, 1997, 278:1041-1042) who specifically teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would believe it more likely than not that the claimed method would function as claimed based only upon the *in vitro* cell culture data disclosed.

Given the clear understanding in the art of the unpredictability of cancer therapy arts, given the known differences between cultured and *in vivo* cancer

cells, given the clear teaching of the unpredictability and unreliability of correlating drug effects *in vitro* with the effects of said drug in cancer patients, it appears that undue experimentation would be required to practice the broadly claimed invention with a reasonable expectation of success

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed methods will function as claimed with a reasonable expectation of success. Again, for the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

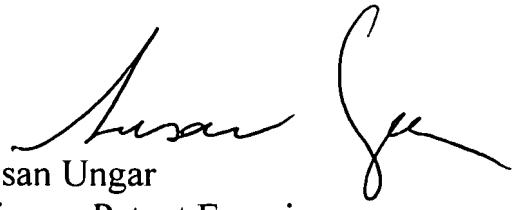
8. Claims 23, 25-26, 28-29, 31, 33 are indefinite and confusing because claim 23 recites "a polypeptide comprising a translated 5' T-box sequence of TBX5 capable of binding to the major groove of target DNA." The claims are confusing because although the translated 5' T-box sequence of TBX5 is required be capable of binding to the major groove of target DNA, it does not appear that the sequence, in the context of the claimed polypeptide, is required to be capable of binding to the major groove of target DNA. Clarification is required.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898.. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Susan Ungar
Primary Patent Examiner
February 12, 2007